UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,152	02/13/2007	Jerome B. Zeldis	9516-313-999	2198

20583 7590 03/10/2009

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
LEWIS, PATRICK T	
ART UNIT	**PAPER NUMBER**
1623	
MAIL DATE	**DELIVERY MODE**
03/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,152	ZELDIS ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 27-50 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 27-50 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 08172007.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 27-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Man et al. US 6,403,613 (Man) and Ignatowski et al. Brain Research (1999), Vol. 841, pages 70-77 (Ignatowski) in combination.

Claims 27-50 are drawn to a method of treating, preventing, modifying or managing pain comprising administering to a patient a therapeutically or prophylactically effective amount of an immunomodulatory compound.

Man teaches 1-oxo- and 1,3-dioxo-2(2,6-dioxopiperdin-3-yl)isoindolines of Formula I decrease the levels of TNFα, increase cAMP levels, and inhibit inflammatory cytokines (column 4, line 36 column 5, line 30). The compounds of Formula I are used, under the supervision of qualified professionals, to inhibit the undesirable effects of TNFα and other inflammatory cytokines including the interleukins IL-1, IL-6, and IL-12. The compounds can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, chemotherapeutic agents, etc., to a mammal in need of treatment; e.g., in the treatment of cancers, rheumatoid arthritis, inflammatory bowel disease, muscular dystrophy, Crohn's disease, etc. The compounds can also be used topically in the treatment or prophylaxis of disease states mediated or exacerbated by excessive TNFα production, respectively, such as viral infections, such as those caused by the herpes viruses, or viral conjunctivitis, psoriasis, atomic dermatitis, etc.

Tumor necrosis factor-α, or TNFα, is a cytokine which is released primarily by mononuclear phagocytes in response to a number of immunostimulators (column 1, line 14 to column 4, line 28). It is a key proinflammatory cytokine in the inflammation

cascade causing the production and/or release of other cytokines and agents. When administered to animals or humans, it causes inflammation, fever, cardiovascular effects, hemorrhage, coagulation, and acute phase responses similar to those seen during acute infections and shock states. TNFα appears to be involved in bone resorption diseases, including arthritis. TNFα is also implicated in the inflammatory response which follows reperfusion, called reperfusion injury, and is a major cause of tissue damage after loss of blood flow. TNFα has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Moreover, it now is known that TNFα is a potent activator of retrovirus replication including activation of HIV-1. Decreasing TNFα levels and/or increasing cAMP levels thus constitutes a valuable therapeutic strategy for the treatment of many inflammatory, infectious, immunological or malignant diseases. These include but are not restricted to septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, opportunistic infections in AIDS, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythrematosis, ENL in leprosy, radiation damage, and hyperoxic alveolar injury.

The carbon atom to which R^3 is bound in the compounds of Formula I constitutes a center of chirality, thereby giving rise to optical isomers (column 7, line 1 to column 8, line 40). Both the racemates of these isomers and the individual isomers themselves, as well as diastereoisomers when a second chiral center is present, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbent. 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline is a particularly preferred compound. The compositions preferably are formulated in unit dosage form, meaning physically discrete units suitable as a unitary dosage, or predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient. Oral dosage forms contain from 1 to 100 mg of drug per unit dosage. Isotonic saline solutions containing from 20 to 100 mg/mL can be used for parenteral administration.

Man differs from the instantly claimed invention in that Man does not explicitly teach the use of the compounds of Formula I for treating pain; although, it is well known that pain is associated with inflammatory conditions such as arthritis. Man also does not explicitly set forth the second active agent, such as clonidine, as instantly claimed. Nonetheless, these differences would have been obvious to one of ordinary skill in the art in view of the teachings of Ignatowski.

Ignatowski teaches that chronic pain syndromes often develop a central nervous system (CNS)-mediated component that plays a role in the cognitive experience of pain and associated mood changes (Introduction). Neuropathic pain develops from intense, prolonged noxious stimulation, or from nerve injury, and leads to long-term functional changes in the CNS, resulting in amplification and persistence of the pain. Drugs that appear to modify adrenergic receptors in the CNS (e.g., clonidine, amitriptyline) are efficacious, to varying degrees, in preventing or alleviating these symptoms. Elevated levels of systemic proinflammatory cytokines occur in association with increases in pain perception, as well as during changes in general mood status. During systemic illness (e.g., rheumatoid arthritis and microbial infections), following activation of the proinflammatory cytokine cascade, patients experience mood changes, such as general malaise and somnolence, along with the appearance of nondescript pain symptoms. A considerable amount of evidence supports a pronociceptive role for TNF during chronic pain. Proinflammatory cytokines, such as TNF, synthesized in neurons within distinct regions of the CNS are involved in promotion neuroplastic changes of noradrenergic neurons involved in the perception of pain. Watkins et al. have proposed that hyperalgesia is produced by the peripheral, local production of proinflammatory cytokines which can activate vagal afferents mediating signals of pain perception to the brain.

Although Man does not explicitly teach the use of 1-oxo- and 1,3-dioxo-2(2,6-dioxopiperdin-3-yl)isoindolines of Formula I for treating, preventing, modifying or managing pain, it would have been obvious to one of ordinary skill in the art to do so

since the relationship between TNFα and pain was well known at the time of the invention. As set forth supra, Ignatowski teaches that chronic pain syndromes often develop a central nervous system (CNS)-mediated component that plays a role in the cognitive experience of pain and associated mood changes. It would have also been obvious to combine the compounds of Man with a second active agent, such as clonidine, which is known to treat or manage pain. All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Thus, one of ordinary skill in the art would have expected that a combination of clonidine and a compound of Formula I as described by Man to be useful for treating, preventing, modifying or managing pain.

Conclusion

5. Claims 27-50 are pending. Claims 27-50 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Patrick T. Lewis/
Primary Examiner, Art Unit 1623

ptl